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Mannich-type Reaction of Methylene Active Compounds with a Chiral Sulfinimine of Trifluoropyruvate: New Highly Stereoselective Synthesis of (S)- α -Trifluoromethyl-Aspartic Acid

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Abstract: A strongly improved, highly stereoselective synthesis of (S)- α -trifluoromethyl aspartic acid via addition of lithium malonate to a chiral sulfinimine of trifluoropyruvate is presented.

Keywords: Fluorine, sulfinimines, Mannich-reaction, α -trifluoromethyl α -amino acids, stereoselective synthesis.

1. INTRODUCTION

There is a growing interest in the field of fluorinated amino acids [1], which hold a great potential for their biological activity as well as for their usefulness in protein engineering [2]. In particular, α -trifluoromethyl (Tfm) α -amino acids are extremely interesting analogues of natural α -amino acids [3], owing to the unique properties of the Tfm group, such as high electronegativity, electron density, steric hindrance and hydrophobic character [4]. A major obstacle in the systematic investigation of the biomedicinal and structural features of α -Tfm α -amino acids, and their peptidic derivatives, has been the relatively difficult availability of most Tfm-amino acids in non-racemic form, whose asymmetric synthesis often requires complex experimental protocols and uneasy to handle starting materials. Non-racemic α -Tfm-aspartic acid (Tfm-Asp) is a target of particular interest, because Asp is a key component of the RGD sequence (Arg-Gly-Asp), which mediates the binding of fibrinogen to its platelet receptor and plays a key-role in a variety of human cerebral and cardiovascular diseases. Recently, we have been involved in a project aimed at the synthesis of RGD peptides incorporating Tfm-Asp [5]. Although many approaches to racemic Tfm-Asp and derivatives have been reported [6], the first synthesis of Tfm-Asp in non-racemic form was described very recently by our group [7] exploiting a stereoselective $\text{TiCl}(\text{O}-i\text{Pr})_3/\text{LDA}$ promoted Mannich-type addition of *tert*-butyl acetate to the sulfinimine [8] of trifluoropyruvate (S)-**2** (Scheme 1).

We now describe a highly efficient, improved approach to (S)-Tfm-Asp in high e.e., exploiting an extremely diastereoselective addition of lithium dimethyl malonate **3a** to (S)-**2**, and a study of the addition of other methylene active compounds **3b-f** to the same sulfinimine (S)-**2**.

2. RESULTS AND DISCUSSION

The enantiomerically pure sulfinimine (S)-**2** (Scheme 1) was prepared, according to the literature method [9], by means of a Staudinger (aza-Wittig) reaction of ethyl trifluoropyruvate with the iminophosphorane (S)-**1**. The Mannich-type reaction of several metalated methylene active compounds **3a-f** with (S)-**2** was addressed next (Table 1).

The lithium malonate **3a** (entry 1) in THF at -78°C added with extremely high stereoselectivity to (S)-**2** producing the diastereomer **5a** in 97% d.e., whereas a certain decrease in stereocontrol was observed using the sodium malonate **3b** (entries 2,3). Chiral HPLC (Chiralcel-OD) showed that the e.e. of **5a** obtained from **3a** was 90% [10]. To our knowledge, this represents the first published example of addition of a β -diester anion to a chiral sulfinimine.

Lithiated acetoacetate **3c** reacted with (S)-**2** with excellent facial diastereocontrol, affording a nearly equimolar mixture of **5b** epimers at the acetoacetate center.

Metalated β -diketones **3d,e** and β -nitroacetate **3f** were also reacted with (S)-**2**, but no formation of the corresponding sulfinamide adducts was detected. As expected, the reactivity of metalated methylene active compounds **3** appears to be proportional to their nucleophilicity, therefore it is higher for metalated β -ketoesters than for β -diketones and β -nitroesters, which are unreactive under the conditions explored so far.

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Scheme 1.

Table 1. ^aA Nearly Equimolar Mixture of Epimers at the C-3 Carbon was Formed. ^bPoorly Soluble in THF at -78°C . ^cMixture of Unidentified Products. ^dDetermined by HPLC Analysis. ^eDetermined by ^{19}F NMR

Entry	Nucleophile 3	Conditions	Ratio 5:4 ^d	Yield (%)
1	3a	LDA, THF, -78°C	5a:4a = 69:1	66
2	3b	NaHMDS, Et ₂ O, -78 to 0°C	5a:4a = 53:1	77
3	3b	NaHMDS, THF, -78°C	5a:4a = 30:1	86
4	3c	LDA, THF, -78°C	5b:4b = >98:2 ^{a,c}	61
5	3d ^b	LDA, THF, -78°C	-	No reaction
6	3e ^b	LDA, THF, -78°C to rt	-	No reaction
7	3f	LDA, THF, -78°C	-	- ^c

The extremely high stereoselectivity of the process could be interpreted by means of the model portrayed in Fig. 1 [11]. Coordination of the sulfinyl oxygen of (S)-2 to the lithium counterion in a six-membered chelate with dimethyl malonate **3a** occurs from the less hindered sulfinimine Re face, with the sulfinyl group and the bulky Tfm in *trans* geometry.

Fig. (1).

Treatment of sulfinamide **5a** (Scheme 2) with trifluoroacetic acid (TFA) in methanol produced the cleavage of the sulfinyl function, affording the free α -amino acid ester (S)-6, along with the co-product *p*-TolSO₂Me. Then, saponification with aqueous KOH at 60°C , followed by purification with an acidic ion-exchange resin DOWEX provided in fair yields the new amino triacid (S)-7 [12]. The

target (S)-Tfm-Asp **8** was obtained from (S)-6 by saponification with KOH at reflux, which also produced decarboxylation of the malonyl moiety, followed by the usual ion-exchange chromatography. Polarimetric analysis of **8** showed positive rotation, with a value in agreement with nearly enantiopure (S)-configured Tfm-Asp [7].

3. EXPERIMENTAL

Reaction of 3a with (S)-2. Dimethyl malonate (132 mg, 3.6 mmol, 1.5 eq.) in dry THF (1 mL) was cooled to -78°C , then a 1.0 M LDA solution in THF (3.6 mL, 3.6 mmol, 1.5 eq) was added dropwise. After 30 min. at the same temperature, a THF (2.0 mL) solution of the sulfinimine (S)-2 (2.4 mmol), prepared *in situ* as previously described [9], was cooled to -78°C , then the above described THF solution of **3a** was added dropwise *via* cannula. After 30 min at -78°C the reaction was quenched with aqueous NH₄Cl, the mixture allowed to warm at rt, extracted with EtOAc, dried over sodium sulfate, filtered and the solvent evaporated at reduced pressure. The crude was purified by flash chromatography (*n*-Hex/EtOAc 3:1)

Scheme 2.

5a. Oil; $[\alpha]_D$ (0.96; CHCl₃) = +68.2; ¹H NMR (200 MHz, CDCl₃): 7.63 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 5.71 (s, 1H), 4.49 (s, 1H), 4.42 (q, J = 7 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.41 (s, 3H), 1.36 (t, J = 7 Hz, 3H); ¹³C NMR (50.3 MHz, CDCl₃): 166.2; 165.4; 164.2; 143.6; 141.8; 129.8; 125.4; 123.0 (q, J = 288.7 Hz); 67.7 (q, J = 28.17 Hz); 64.2; 53.6; 53.5; 53.0; 21.4; 13.7.

4. CONCLUSION

In conclusion, we have developed an extremely efficient and simple, highly stereoselective synthesis of (S)-α-Tfm-aspartic acid **8**, which can be obviously extended to the (R)-enantiomer starting from (R)-**2**, in high e.e. exploiting a stereocontrolled Mannich-type reaction of lithium malonate with a chiral sulfinimine of trifluoropyruvate. The addition of further methylene active nucleophiles to (S)-**2** is currently under investigation.

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REFERENCES AND NOTES

- [1] Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711.
- [2] Kim, W.; George, A.; Evans, M.; Conticello, V. P. *Chem. Bio. Chem.* **2004**, *5*, 928. (b) Tang, Y.; Ghirlanda, G.; Petka, W. A.; Nakajima, T.; DeGrado, W. F.; Tirrell, D. *Angew. Chem. Int. Ed.* **2001**, *40*, 1494. (c) Duwel, H. S.; Daub, E.; Robinson, V.; Honek, J. F. *Biochemistry* **2001**, *40*, 13167. (d) Wang, P.; Tang, Y.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 6900. (e) Niemz, A.; Tirrell, D. A. *J. Am. Chem. Soc.* **2001**, *123*, 7407. (f) Bilgic, B.; Fichera, A.; Kumar, K. *J. Am. Chem. Soc.* **2001**, *123*, 4393. (g) Horng, J.-C.; Raleigh, D. P. *J. Am. Chem. Soc.* **2003**, *125*, 9286. (h) Arai, T.; Imachi, T.; Kato, T.; Nishino, N. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 439. (i) Wang, P.; Fichera, A.; Kumar, K.; Tirrell, D. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3664.
- [3] *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A. Eds.; Wiley: Chichester, 1995. (b) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, 621.
- [4] Banks, R. E.; Tatlow, J. C.; Smart, B. E. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, **1994**.
- [5] Dal Pozzo, A.; Muzi, L.; Moroni, M.; Rondanin, R.; de Castiglione, R.; Bravo, P.; Zanda, M. *Tetrahedron* **1998**, *54*, 6019. (b) Dal Pozzo, A.; Dikovskaya, K.; Moroni, M.; Fagnoni, M.; Vanini, L.; Bergonzi, R.; de Castiglione, R.; Bravo, P.; Zanda, M. *J. Chem. Res.* **1999**, 468.
- [6] Soloshonok, V. A.; Gerus, I. I.; Yagupol'skii, Yu. L.; Kukhar', V. P. *J. Org. Chem. USSR (Engl. Transl.)* **1987**, *23*, 2034. (b) Kobzev, S. P.; Soloshonok, V. A.; Galushko, S. V.; Yagupol'skii, Yu. L.; Kukhar', V. P. *J. Gen. Chem. USSR (Engl. Transl.)* **1989**, *59*, 801. (c) Osipov, S. N.; Kolomiets, A. F.; Fokin, A. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1989**, *38*, 673. (d) Burger, K.; Gaa, K.; Geith, K. *J. Fluorine Chem.* **1988**, *41*, 429. (e) Sewald, N.; Riede, J.; Bissinger, P.; Burger, K. *J. Chem. Soc. Perkin Trans. 1* **1992**, 267. (f) Laurent, P.; Henning, L.; Burger, K.; Hiller, W.; Neumayer, M. *Synthesis* **1998**, 905.
- [7] Lazzaro, F.; Crucianelli, M.; De Angelis, F.; Frigerio, M.; Malpezzi, L.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **2004**, *15*, 889.
- [8] For a review of sulfinimine chemistry see: Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.
- [9] Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; García Soler, J.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449. (b) Bravo, P.; Vergani, B.; Crucianelli, M.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771.
- [10] A slight racemization of the sulfinimine (S)-**2** appears to take place during the malonate addition, as already observed in the reaction with some enolates, as well as with alkyl, benzyl and allyl Grignard reagents (see Ref. 7 and 9).
- [11] Mioskowski, C.; Solladié, G. *J. Chem. Soc., Chem. Commun.* **1977**, 162.
- [12] Compound **7** was found to be stable for several months when stored at 4 °C, otherwise slow spontaneous decarboxylation to **8** was observed.